

### Remarks

Support for the Claim amendments is as follows:

Claim 4A is based on original description of invention on page 6 lines 5-7; Claim 4B is from original claim 1 part D.

Support for Claim 22A: pg 7: lines 1-4: "A given node may encompass many signature sequences. Likewise, a particular test sequence can be a signature encompassed by more than one node, though frequently with differing values of Q s. This reflects the child, parent, grandparent or other taxonomic relationship between bifurcation nodes on a phylogenetic tree.

Claim 4C has been further amended to emphasize that "...the number of organisms or viruses whose genetic affinity might be determined is at least twice the number of probes used" . This further distinguishes from Barns, as in the instant invention the probes, once chosen, can be used to determine the genetic affinity of many organisms or viruses and targeted at once to many organisms and viruses whereas in Barns a new set of probes is required for each target grouping

This is supported in the Specification on page 7 lines 12-14 by the statement "It is contemplated that this invention can allow the development of a single test system that can be used to identify a wide range of organisms." Also page 7 line 8: "Thus it is possible to replace many tests with just one". In addition, Table G indicates that the most preferred number of probes is 50-10,000. The ribosomal RNA database has more than 10,000 organisms in it, implying we use fewer probes than the number of organisms whose genetic affinity we can determine.

[Claim 8 parsimony methods were elected 27Apr 06, see "Interview", above.]

Claim 19 Additional items are supported by table G on pg 58, p6 lines 1-3

Claim 21 is supported in the original specification on - Table G examples 9 and 11, pg 8 line 7-8, pg 30 line 28-29.

Claim 23 is supported in the original specification in Table G p30 line 35, p30 line 29, p 8 line 6, pg 7 line 16-18, pg 33 line 17)

Claim 24 is supported on p 33, lines 15-17 of the application.

Claim 30 is supported by Table G.

New Claim 37 is supported at Table G, Pg 30 line 35; pg 30 line 29; pg 8 line 6; pg 7 line 17; pg 33 line 17. Support for Claim 22A: pg 59 Table 2 for many specific genetic groupings, e.g. kingdom, phylum, class, order, family, genus, species, subspecies, etc.

Support for Claim 37B: Multiple groupings in a single probes set are supported on page 7 lines 12-14 by the statement "It is contemplated that this invention can allow the development of a single test system that can be used to identify a wide range of organisms." Also page 7 line 8: "Thus it is possible to replace many tests with just one".

Support for Claim 37B: Varying signature quality, Qs, is mentioned in numerous places where the Specification states that probes of different signature quality are used at same time.

Support for Claim 37F: Verification & parent & grandparent are supported best in Example 2, page 25 lines 18-22: "... the correct neighborhood is readily identified by the presence of multiple hits whereas the noise placements are frequently loners. This is a very important aspect of the method, which stems directly from the parent/child relationship between nodes in a bifurcating tree. Thus, false positives are not a serious impediment to success. False negatives are also not a problem because of the redundancy of signature sequences that occur at many nodes"

Claim 38 is supported at Page 31, Lines 22-32.

Claim 39 is supported at Page 5 lines 31-37.

For convenient reference, the Detailed Action is reproduced below with responses interspersed between paragraphs.

**DETAILED ACTION**

*During a telephone conversation with Richard Coale Wilson on 4/27/2006 a provisional species election was made for species of parsimony methods without traverse to prosecute the invention of inventive group II, claims 4-10 and 19-20.*

*Affirmation of this species election must be made by applicant in replying to this Office action.*

That species election is affirmed. Please note the attorney's name is "Willson".

*Applicant's election of group II, claims 4-10 and 19-20, in the reply filed on 2/17/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant's amendment of claim 20 now depends from and is being drawn to non-elected inventive group with specifics of claim I (Group I), which are distinct from the claim 4 (Group II) signature probe practice and has thus been withdrawn. Claims 1-3 and 11-18, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventive group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election requirement in the reply filed on 2/17/2006.*

Claim 20 has been amended entirely.

***Claim Objections***

*Claim 10 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must be written in the alternative only. Claim 10 is a multiple dependent claim depending from claims 1 and 4, but not written in the [Page 3] alternative and therefore is not compliant with the guidelines for writing multiple dependent claims. See MPEP § 608.01 (n). Accordingly, the claim has not been further treated on the merits.*

It is respectfully urged that Claim 10 is not a multiple dependent claim. It merely incorporates the wording of Claim 1 (withdrawn). Claim 10 is now amended by transcribing that wording into Claim 10. If any Multiple Dependent Fee has been charged against this application, it should be refunded.

***Claim Rejections - 35 USC § 112***

*The following is a quotation of the second paragraph of 35 U.S.C. 112:*

*The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.*

*Claims 4-9 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.*

*Claim 4 recites the limitation "the bifurcating tree of genetic relationship" in step D. There is insufficient antecedent basis for this limitation in the claim.*

Claims 5-9 and 19 are rejected as being dependent from a rejected claim.

Claim 4 now recites the proper antecedent basis.

*Claim Rejections - 35 USC § 103*

*The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:*

*(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.-9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes et al. (US Pat 5217862) in view of Barbour et al. (US Pat 5,932,220).*

*[Page 4]*

"Barns" is the correct spelling of the inventor of US 5,217,862.

*Barnes et al. teaches step A of the method of Claim 4 at p. 4, col. 5, lines 50-68 and col. 6, lines 1-15, where the tables are the database of signature sequences from which the signature probes are aligned or derived as required by step A of Claim 4.*

*Barnes et al. teaches step B of the method of Claim 4 at p. 4, col. 5, lines 18-45, where the signature probes are modified as signal-carrying probes or to carry detection ligands, such as fluorescein, as required by step B of Claim 4.*

*Barnes et al. teaches steps C-E of the method of Claim 4 and 9 at p. 4, col. 6, lines 20-68 and p. 5, col. 7, lines 1-34 describe using a phylogenetic relationship to identify the closest known genetic relatives of the organism. Additionally, Barnes et al. teaches identifying the organism in the test sample that is within the most terminal node as supported by the signature probes in the dot blot hybridization tests as required in steps D and E of Claim 4. Barnes et al. describes using the dot blot hybridization and building of a phylogenetic relationship tree with respect to a specific species of bacterium.*

*Barnes et al. teaches Claim 5 requirements of the signature probes comprising particular biological material at p. 3, col. 4, lines 27-39, where Barnes et al. describes the signature probes comprising DNA or RNA sequences.*

*Barnes et al. teaches Claim 6 and 7 hybridization utilizing an immobilized array of signature probes along*

*with a detection step utilizing radioactive,  
chemiluminescence and/or fluorescence at p. 6, col. 6,  
lines 21-61.*

The rejection on Barns must be traversed. Barns' only independent Claim reads:

1. A method of detecting the presence of *Neisseria gonorrhoeae* in a sample comprising: ...

Thus, Barns does not offer a method for analyzing *what* is in the sample, only whether or not *Neisseria gonorrhoeae* is present. In contrast, the powerful present invention determines the genetic affinity of any organism or virus in the sample. Indeed, it is not even necessary that the organism had been encountered previously by the scientific community. This is possible because the Applicant's method focuses on genetic affinity (closest relatives among previously studied organisms) rather than specific identity. In contrast, Barns not only focuses on specific identity but only does it for one specific organism *Neisseria gonorrhoeae*. Even if it were possible to successfully apply the method of Barns to every known organism [*Barns* (p. 4, col. 6, lines 28-31) teaches that "demonstrating exclusivity for any given probe sequence is not only unpredictable but extremely difficult and laborious"], Barns' method would still fail if a previously unstudied organism or unknown organism were encountered. These differences between Barns and the Applicant's invention seem analogous to the difference between litmus paper and a mass spectrometer!

Barns' sole independent claim continues to be specific to detecting a *single* type of bacterium throughout Barns' remaining steps a), b) and c):

- a) contacting said sample with a nucleic acid probe which preferentially hybridizes to rRNA or rDNA of *Neisseria gonorrhoeae* over rRNA or rDNA of non-*Neisseria* bacteria, wherein said probe is complementary to a region of the *Neisseria gonorrhoeae* 16S rRNA selected from the group of regions consisting of the region 455 through 477 and the region 983 through 1010, and the region of the *Neisseria gonorrhoeae* 23S rRNA selected from the group of regions consisting of the region 89 to 116 and the region 156 to 182;
- b) imposing hybridization conditions on said sample and the nucleic acid probe to allow the nucleic acid probe to hybridize to the rRNA or rDNA of *Neisseria gonorrhoeae*, if present in said sample, to form hybridized nucleic acid complexes, under conditions which do not allow said nucleic acid probe to form stable hybridized nucleic acid complexes with non-*Neisseria* rRNA or rDNA; and
- c) detecting said hybridized nucleic acid complexes as an indication of the presence of said *Neisseria gonorrhoeae* in said sample.

Barns teaches a method to obtain organism-specific probes which have favorable properties [Note Barns' Tables 3 and 4]: Barns uses the terms "inclusivity" (essentially all of the target organisms have the particular sequence) and "exclusivity" (the sequence under consideration is highly unlikely to be found outside of the target group). Barns teaches away from the present invention by emphasizing the importance of having extraordinary inclusivity and exclusivity for a particular species (p. 3, col 5, lines 29-31; and p.4, col 6, lines 1-15).

By requiring probes with "extraordinary" inclusivity and exclusivity at the species level Barns is requiring that the signature quality index,  $Q_s$ , [page 11 lines 10-15] of the present invention be either 1 (perfect signature) or extremely close to one for the sequences to be useful. However, in the

present invention the values of Qs can be much lower than the values at which Barn's inclusivity and exclusivity become useful. For example,  $Q = 0.7$  is useful to us, but not to Barns. By suggesting very high Qs values are essential, Barns teaches away from the present invention which teaches instead that sequences with modest signature quality scores can be very useful. The present invention does not prefer Barn's inclusivity and exclusivity i.e.  $Qs = 1.0$  because at  $Qs = 1.0$ , many groupings would have no useful signature sequences and hence not be recognizable. In addition, useful probes will have differing non unitary Qs values for multiple related groupings (child, parent, grandparent, etc) (pg 7 lines 3-4). Moreover, sequences which have moderate Qs scores for multiple unrelated groupings can be especially helpful in designing an assay with a minimal number of probes using overlapping information. Thus, Barns teaches discarding many of the preferred probes of the present invention, which have Qs values well below 1.

Signature sequences are informative about the genetic affinity of the organism or virus carrying the nucleic acid. They are absolutely not required to have either Barns' inclusivity or Barns' exclusivity, and in fact, it can be best if they do not have either. Thus, p. 7 line 1 of the Application indicates that the invention works to "retain as signature sequences those test sequences having values of Qs above some criterion". That criterion need not be 1 or even close to 1. For example, a signature sequence may occur in 90% of the organisms or viruses in one grouping, 70% of the organisms or viruses in another grouping and 45% in a third grouping. It would thus have a different Qs score for each grouping and each of these scores would be well below the perfect score of 1.0. (see p. 7, lines 1-4, and p. 22 lines 1-2 of

the Applicant's application). That one can use such N-mers (subsequences) according to the present invention is extremely unexpected and non-obvious. Barns (p. 3, col. 5, lines 29-31; and p.4, col. 6, lines 1-15), teaches that subsequences exhibiting poor exclusivity and inclusivity (that is sequences with lower Qs scores) are *not useful*. In contrast, the present invention teaches that such sequences with signature quality scores well less than perfect can in fact be very useful. For instance, in the example given above they contribute to the recognition of three distinct organism or virus groupings rather than just one. In order to take advantage of the information carried by such signature sequences, the present invention ( p.7 lines 9-11) teaches the use of a "plurality" of such signature probes that target many separate groupings, not just one. One important result of this is an inherent check on reliability of the final answer (p 7 lines 2-4 of the Applicant's application) in that a positive result for a child node would be expected to be associated with positive signals for various genetic antecedents such as parent, grandparent etc. Thus, if an organism gave a signal suggesting it was similar to *Bacillus anthracis*, it would be expected to give signals for many genetic antecedents such as the genus *Bacillus*, the family Bacillaceae, the order Bacillales, the Class Bacilli, and the Division Firmicutes.

According to the present invention, appropriately designed assays (especially those using arrays p 61 line 11 of Applicants application) or mass spectrometric methods (p. 7 lines 16-17 of Applicants application)) based on signature sequences with only modest Qs scores require information from far fewer signature sequences than one might otherwise expect. For example, a hybridization array using signature probes to determine the genetic affinity of 50,000 distinct bacterial genera can require far less than



50,000 probes. This is because a large number of unique hybridization patterns are generated by the probes, when each probe is indicative of multiple groupings.

Barns still further teaches away from the present invention by describing methodology to recognize a *specific member* of a taxonomic group of *a priori* interest. On p. 4, col. 6 lines 20-25 Barns describe looking for regions of ribosomal RNA that would recognize a specific organism of interest. This is opposite to the present method which instead teaches looking at every N-mer (subsequence), not to determine if it is a suitable probe target (as used by Barns.) but instead to determine what its particular signature properties are (p. 6 lines 14-18 of Applicant's application). In fact, it is preferable in the Applicants' invention not to consider sequences that have perfect sequence quality for a single species. Note p. 6 lines 16-20 where the Applicants state "It is preferable and computationally efficient to only calculate the Qs values for test sequences of length N that occur at least twice in the database." In essence then, since Barns advocates the use of the very sequences that Applicants suggest discarding in the present invention, it is incorrect to assert that the sequences identified by the methods described by Barns (p. 4, col. 6, lines 20-68 and p. 5, col. 7, lines 1-34) are equivalent to the signature sequences meant in the Applicant's invention.

Specifically, Barns only considers sequences with very high Qs scores and then for only one predetermined node in the tree. In contrast, the Applicant's invention can consider all sequences with a non zero Qs score separately not for one but rather for every node in the tree. Hence, it is inappropriate to

assert that the sequences being identified by Barns are equivalent to the sets of signature sequences used in the Applicant's invention.

In contrast to Barns, the present invention instead teaches a valuable method to determine the genetic affinity of completely unknown bacterium or virus without prior knowledge of what might be encountered. This is accomplished by including signature probes such that, depending on the number of probes used and the particular organism that is actually encountered, the genetic affinity determined may be at a low taxonomic level ( e.g. Order) or at a high level (e.g. genus or even species). The present method is thus valuable in situations such as a possible terrorist attack where it would be important to quickly obtain insight to the identity of a completely unknown organism or virus. The invention described by Barns does not have this important utility.

Step D of newly revised claim 4 (step B of original claim 4)

The modified probes described by Barns (p. 4, col. 5, lines 18-45) are required to have perfect inclusivity (p. 4, col 5, line 18-20) or very high exclusivity (p. 4, col 5, line 20-25). In terms of the present invention this amounts to considering only those N-mers with very high or perfect Q s scores and hence does not include most of the preferred signature probes that are considered in the Applicant's invention. Moreover, the invention of newly revised claim 4 is unique in combination with steps A, B, C, D, E, and F.

Steps E-G of newly revised claim 4 (steps C-E of original claim 4).

The modified probes described by Barns (p. 4, col. 5, lines 18-45) target subsequences of the target nucleic acid that have either have perfect "inclusivity" (p. 4, col 5, line 18-20) or very high "exclusivity" (p. 4, col 5, line 20-25) In terms of the present invention, this amounts to considering only those N-mers with very high or perfect Q s scores and hence does not include most of the preferred signature probes that are considered in the Applicant's invention. Thus, Barns does not teach a method for identifying the types of signature sequences required by the Applicant's invention. The purpose to which Barns is using phylogenetic information is different than in the instant invention. Their objective is to use the phylogenetic information to determine (p. 4, col. 6, lines 36-45) which sequence to best compare to the sequence of their pre-selected target organism *Neisseria gonorrhoeae*. In the Applicant's invention, the purpose of having (or obtaining- Claim 8) relationship information is to characterize the signature properties (if any) of every candidate signature sequence. In contrast to Barns, no specific organism is examined with respect to any candidate signature sequence.

In addition, in the section cited by the examiner, (p. 4, col. 6, lines 28-31) *Barns* again teaches away from the Applicant's invention by stating that "demonstrating exclusivity for any given probe sequence is not only unpredictable but extremely difficult and laborious". It is implicit in this statement that sequences deficient in exclusivity, e.g. low Qs values must be avoided because they are not useful. In contrast, the Applicant's invention teaches that the lack of or limited exclusivity (low Qs value) does not disqualify a signature sequence from use. Hence not only does Barns . teach away from the current invention but their statement demonstrates that it is

neither obvious nor expected that one could usefully use N-mers that lack Barns type exclusivity (i.e. low Qs scores).

Also, it should be noted that the signal obtained by the present invention when implemented as an array of signature probes (p 61 line 11 of Applicants application) will typically not be a single yes/no for specific probes as in the method of Barns but instead it will be a complex pattern. If two different organisms are separately subjected to the procedure of the invention, they may produce a pattern that overlaps because some of the probes based on signature sequences will be positive in both cases because the sequences are in the same grouping at some phylogenetic level (p. 7 lines 2-4). For example *Staphylococcus* and *Bacillus* will both likely trigger probes that are signatory of the Division Firmicutes. However, some probes based on signature sequences may test positive for multiple taxonomic units that are not phylogenetically contiguous ( e.g. Gamma Proteobacter and Bacillaceae). Such a probe would tell us that the unknown organism is likely not a cyanobacterium but it could easily still reflect the presence of either *Escherichia coli* or *Bacillus subtilis*. The full meaning of a positive result for this particular probe would only be determined in the context of the results obtained for all the other probes in the array.

Finally, the invention of newly revised claim 4 is unique in combination with steps A, B, C, D, E, and F.

Step E-F of newly revised claim 4 (steps DE of original claim 4)

Again, the modified probes described by Barns (p. 4, col. 5, lines 18-45) target subsequences of the target nucleic acid that have either have perfect inclusivity (p. 4, col. 5, line 18-20) or very high exclusivity (p. 4, col. 5, line 20-25) In terms of the present invention, this amounts to considering only

those N-mers with very high or perfect Q s scores and hence does not include most of the preferred signature probes that are considered in the Applicant's invention. Moreover, the invention of claim 4 is unique in its combination of steps A, B, C, D, E, and F

It is explicit in step D of the original claim 4 (step F of the revised claim 4) and implicit in step C of the original claim 4 (step D of the revised claim 4) that multiple, not single, signature probes will produce the signal. Thus, if the terminal identification of an unknown organism is to a particular genus there must also be positive signals supporting its membership in the appropriate broader phylogenetic groupings, e.g. Order, Class, etc. In contrast, the method of Barns focuses exclusively on a single specific taxonomic level and a specific species of bacterium.

#### **Claim 5**

As outlined above, Barns does not teach the method of Claim 4 upon which claim 5 is dependent.

In addition, as discussed with reference to claim 4, the modified probes described by Barns (p. 4, col. 5, lines 18-45) target subsequences of the target nucleic acid that have perfect inclusivity (p. 4, col. 5, line 18-20) and very high exclusivity ) (p. 4, col. 5, line 20-25). In terms of the present invention, this amounts to considering only those N-mers with very high or perfect Q s scores and hence Barns does not include most of the preferred signature probes that are considered in the Applicant's invention. Hence, the probes referred to on p. 3, col. 4 lines 27-39 are not based on signature sequences as intended in the Applicant's invention and the discussion on the

indicated lines is not applicable to the present invention as claimed in Claim 5.

#### **Claims 6 and 7**

As outlined above, Barns does not teach the method of claim (4) upon which claims 6 and 7 are dependent.

In addition, as discussed with reference to claim 4, the modified probes described by Barns (p. 4, col. 5, lines 18-45) target subsequences of the target nucleic acid that either have perfect inclusivity (p. 4, col 5, line 18-20) or very high exclusivity (p. 4, col 5, line 20-25). In terms of the present invention, this amounts to considering only those N-mers with very high or perfect Q s scores and hence does not include most of the preferred signature probes that are considered in the Applicant's invention. Hence, the probes referred to on p. 6, col. 6 lines 21-26 are not based on signature sequences as considered in the Applicant's invention and therefore the discussion on the indicated lines is not directly relevant to the present invention.

#### **Claim 19**

As outlined above, Barns does not teach the method of claim 4 upon which claim 19 is dependent.

In addition, as discussed with reference to claim 4, the probes described by Barns (p. 5, col. 7, lines 35-66) target subsequences of the target nucleic acid that have either perfect inclusivity (p. 4, col 5, line 18-20) or very high exclusivity (p. 4, col 5, line 20-25) In terms of the present invention this amounts to considering only those N-mers with very high or perfect Q s scores and hence does not include most of the preferred signature probes that

are considered in the Applicant's invention. Hence, the probes referred to on p. 6, col. 6 lines 21-26 of Barns are not based on signature sequences as considered in the Applicant's invention and therefore the discussion on the indicated lines is not directly relevant to the present invention.

#### **Claim 22**

22 A- states the invention with less emphasis on the role of a tree in primary claim 4 as it is knowledge of genetic relationships that is essential to the invention not a particular tree. Claim 22A distinguishes from Barnes by emphasizing that the invention looks at many levels of genetic affinity not just one.

22 B: Distinguishes from Barnes by indicating that the invention does not require high inclusivity or exclusivity. Claim 22B also emphasizes that the invention identifies multiple groupings with a single set of probes while Barnes can only look for one grouping at a time.

22 C: Emphasizes that, in contrast to Barnes, the invention does not look for a specific target organism

22 F: This additional step adds even further distinction from Barnes. Barnes does not teach the step of verifying that a positive *Neisseria gonorrhoeae* probe is true by showing that the organism also gives a positive result with a second distinct probe that should be positive with any *Neisseria* strain

"Distinct" here refers to the fact that although single false positive probe to a species will necessarily hit some ancestors too but other probes that should hit the same ancestors will not.

*Claim 19 recites the phrase "fragment of the foregoing." This phrase has been interpreted to mean a fragment of either of the reference DNA regions prior to using this [Page 5] phrase; the DNA fragment could either be from the spacer region between ribosomal RNA genes or a fragment of the ribosomal RNA genes. Barnes teaches using signature probes of length 6 or larger at p. 5, col. 7, lines 35-66 where the physical description of the probes is discussed. Additionally, Barnes teaches isolating the nucleic acid from ribosomal RNA genes at p. 4, col. 6, lines 55-69 and p. 5, col. 7, lines 1-34.*

*Barns. does not specifically teach a sequence analysis using parsimony methods.*

*Barbour et al. teaches doing a sequence analysis using parsimony methods at p.18, col. 29, lines 23-42.*

*It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the parsimony method of sequence analysis taught by Barbour et al. to the creation of signature probes using phylogenetic analysis taught by Barnes. because using a parsimony method is very suitable*

*for an analysis of sequences which are quite similar. Therefore, when creating probes that need species specific designing, then a careful analysis of very similar sequences is required. In addition, when determining an evolutionary tree of related organisms, the parsimony method not only creates an evolutionary tree, but also examines all possible evolutionary trees to result in the most probable phylogenetic tree.*

Adding Barbour to Barns, even with improper hindsight, does not make the invention obvious under 35 U.S.C. 103. Barbour teaches the parsimony method of inferring evolutionary relationship between organisms from nucleic acid sequences. This is not unique to Barbour, as the technique is taught in any textbook on molecular evolution. Barbour describes the use of the parsimony method to analyze extremely similar sequences. Even if Barbour's methodology were used in conjunction with the methods of Barns, as the examiner suggests above with reference to Claim 4, the probe target sequences obtained by Barns would not be the signature sequences taught in this application. In addition, applicants' bifurcating tree, described in Claim 4, defines the genetic framework that an unknown organism or virus can be related to (genetic affinity). Thus, applicants' tree construction is not only for very closely related organisms as in Barbour. Instead in the instant invention the purpose of the tree is to provide a definition of genetic affinity that the information carried by each candidate N-mer (subsequence) can be correlated with. Moreover, in Applicants' invention, it is not necessary to use the specific sequences that give rise to the candidate signature sequences to construct the tree of relationship. For example, when designing signature probes that target 23S ribosomal RNA one might use a database of 16S rRNA sequences to construct the tree of genetic relationship.

Conclusion: Claim 37 has been added to further clarify and differentiate from Barns. Neither Barns nor Barbour even imagines the unexpected



advantage achieved by the present invention, so it is not sustainable to reject the invention as being made obvious by a combination of two references, neither of which attains or suggests its results.

[Page 6]

*Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason Sims, whose telephone number is (571)-2727540. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ardin Marschel can be reached via telephone (571)-272-0718.*

*Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (571)-273-8300.*

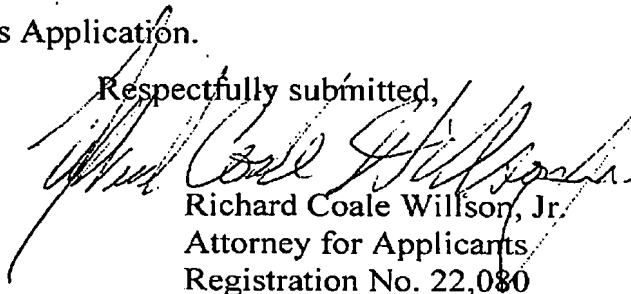
*Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571)-272-0549. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).*

ARDIN H. MARSCHEL  
SUPERVISORY PATENT EXAMINER

The one-month extension fee and any other necessary (small entity) charges can be charged to USPTO Deposit Account 20-336 of Technology Licensing Co. LLC. Correspondence may be addressed to Customer No. 26830.

The Examiner is especially invited to suggest allowable subject matter on next action, and to telephone Applicants' Attorney if that would expedite prosecution and disposal of this Application.

Respectfully submitted,



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